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Impact of Lower Urinary Tract Symptoms on Mortality: A 21-Year Follow-up among Middle-aged and Elderly Finnish Men

Authors

Jonne Åkerla[a,b*], Jori S Pesonen[c,d], Antti Pöyhönen[a], Jukka Häkkinen[e], Juha Koskimäki[d], Heini Huhtala[f], Teuvo L.J. Tammela[b d], Anssi Auvinen[f]

Author affiliations

[a] Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland

[b] Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

[c] Department of Surgery, Päijät-Häme Central Hospital, Lahti, Finland

[d] Department of Urology, Tampere University Hospital, Tampere, Finland

[e] Department of Urology, Turku University Hospital, Turku, Finland

[f] Faculty of Social Sciences, University of Tampere, Tampere, Finland

* Corresponding author: Jonne Åkerla, M.D., Department of Surgery, Central Finland Central Hospital; Keskussairaalantie 19, 40620 Jyväskylä, Finland; tel. +35814 2695068; jonne.akerla@fimnet.fi; fax. +35814 2692783

Running title: LUTS and mortality among aging men

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Abstract

Background: The usefulness of lower urinary tract symptoms (LUTS) as mortality risk factors remains unclear. Repeated assessments are required to take into account symptom fluctuation and *de novo* symptom appearance. The study objective was to evaluate mortality in relation to three urinary storage symptoms — urgency, daytime frequency and nocturia — in middle-aged and elderly men, considering also other time-varying factors during follow-up.

Methods: A mail survey of a population-based cohort of men initially aged 50, 60 and 70 years was conducted in Finland in 1994, 1999, 2004 and 2009. The questionnaire included assessments of LUTS based on the Danish Prostatic Symptom Score and comorbidities. The men were followed up for mortality through the population registry through 2014. LUTS-related hazard ratios (HR) were analyzed with time-dependent Cox regression adjusted for the year of birth and comorbidities using variable values updated every five years. Sensitivity analyses were conducted using values of all variables fixed to the baseline assessment of 1994.

Results: Of the 1332 eligible men with data on LUTS from each preceding survey, 514 (38.6%) died during the 21-year follow-up. In time-dependent analyses, daytime frequency and nocturia were significantly associated with increased mortality: the adjusted HR was 1.42 (95%CI 1.11-1.83) for daytime frequency, 1.38 (1.07-1.79) for nocturia and 1.19 (0.94-1.50) for urgency. In sensitivity analyses with fixed baseline characteristics, only nocturia was suggestively associated with an increased risk of death: the adjusted HR was 1.09 (0.84-1.42) for daytime frequency, 1.41 (0.99-2.02) for nocturia and 0.94 (0.52-1.68) for urgency.

Conclusions: Among aging men**,** LUTS are more accurate predictors of short-term than longer-term mortality risk. Repeated assessments are needed to detect clinically

relevant and persistent symptoms, often associated with ill health. Accordingly, men with daytime frequency or nocturia exhibit a 1.4-fold risk of death and therefore, should be evaluated for underlying comorbidity.

Introduction

The number of patients presenting with lower urinary tract symptoms (LUTS) is increasing as the population ages. LUTS are divided into two broad categories: storage symptoms (daytime urinary frequency, nocturia, urgency, urinary incontinence) and voiding symptoms (incomplete emptying, intermittency, slow stream, hesitancy). An important factor for male LUTS is bladder outlet obstruction (BOO), typically caused by benign prostatic hyperplasia (BPH) — a condition affecting more than half of men aged over 50 years [1]. Although various interventions can alleviate bothersome LUTS, persistent or recurrent symptoms are frequent despite treatments such as surgery for BOO [2,3]. This is explained by the multifactorial etiology of LUTS: age-related physiological changes, various lifestyle factors and medical conditions affect lower urinary tract and renal function. Of the various LUTS, comorbidities are particularly important for urinary storage symptoms [4,5].

As men with LUTS tend to be older and are more likely to have comorbidities than asymptomatic men, they are potentially at a higher risk of death. To reliably assess the impact of LUTS on mortality, careful consideration of various confounding factors is warranted. Longitudinal studies have suggested LUTS to predict development of cardiovascular diseases, albeit with some inconsistency [6,7]. In previous longitudinal studies, LUTS have commonly been assessed either by using pre-defined cutoff values of various symptom scores or by retrospectively screening medical records for diagnosis codes without distinguishing individual symptoms. In the case of nocturia — the only symptom for which an association with mortality has been addressed in several earlier studies — the heterogeneity among previous results may reflect variation in methods, follow-up times and age distributions [8], as the natural course

of LUTS may vary considerably between populations [9-11]. Hypothetically, the confidence of the estimates on LUTS-related mortality could be strengthened by taking into account the incidence and remission of symptoms and comorbidities in the course of follow-up. Therefore, the aim of this study is to analyze the impact of three common storage LUTS – urinary urgency, daytime frequency and nocturia – on all-cause mortality during 21 years of follow-up utilizing repeated assessments in a population-based cohort of middle-aged and elderly men

Subjects and Methods

Tampere Aging Male Urologic Study

A population-based cohort study focusing on urological symptoms and sexual functioning among middle-aged and elderly men was launched in Pirkanmaa County, Finland in 1994, with repeat rounds in 1999, 2004 and 2009. Study details have been published previously [12,13]. Briefly, a sample of 3143 men was identified from the Finnish Population Register in 1994, comprising all men born in 1924, 1934 or 1944 residing in the study area at the baseline. Self-administered questionnaires were mailed to the men in the study population at all rounds. Non-responders were reminded with a second mailing after three months. The questionnaire comprised items on frequency and bother of LUTS, major health conditions and medications, as well as sociodemographic, anthropometric, and lifestyle factors. An exemption from ethical review was granted by the ethics committee of the Pirkanmaa Hospital District (tracking number 99050).

Measures

The frequencies of LUTS were assessed using the Danish Prostatic Symptom Score (DAN-PSS-1) [14], consistent with the International Continence Society definitions [15]. An exception was made in 1994 in the assessment of urgency, where a modified question translated back from Finnish to English was as follows: “Is your need to urinate so urgent that it is difficult to hold it back until you reach the toilet?”, which was since modified and used at subsequent the rounds in 1999, 2004 and 2009 as “Do you experience an imperative (strong) urge to urinate?”. The response options were never—rarely—often—always. The question concerning daytime frequency was “What is the longest interval between each voiding, from when you wake up until you

go to bed?" with response options of more than 3 hours—2-3 hours—1-2 hours—less than 1 hour. The question concerning nocturia was "How many times do you have to urinate per night?" with response alternatives of none—1 or 2 times—3 or 4 times—5 times or more. The preceding four-week period was used as the reference time frame for the questions. As only moderate and severe LUTS are clinically meaningful, these were compared with mild or absent symptoms after recoding each symptom into a binary variable [16]. Accordingly, urgency was categorized asFor the analysis, each symptom was recoded into a binary variabl "e:often or always" vs. "never or rarely" and daytime frequency as nine or more vs. eight or less voids per day. Based on the response alternatives for nocturia question in DAN-PSS, the case definition of three or more vs. two or less voids per night was considered to most adequately detect
clinically relevant cases with best comparability to the generally acknowledged case definition for significant nocturia of two or more more voids per night [8,17]. no or mild vs. moderate or severe symptoms (the first two versus the two latter options). The men were followed up for mortality through the population registry until the end of 2014. Information on the time and cause of death was obtained by a deterministic linkage with the unique personal identification number as the key.

Statistical Analyses

For analyses of mortality, we included men who had answered questions for LUTS at every survey in 1994-2009 (while alive) and for comorbidities at least in the 1994 survey. To adjust the analyses for confounders, variables with well-established prognostic importance were selected for regression analyses. These variables, of which many are also known to be associated with LUTS, included age, marital status (married or cohabiting versus single or widowed), body mass index (BMI , ≤25 versus

>25 kg/m^2), current smoking (yes/no), alcohol consumption (≤150 g/week vs. >150 g/week), previous diagnosis of diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, cancer and neurological disease.

Univariate Cox regression analyseis weares performed for each urinary symptom and potential prognostic variable. To assess their independent effects on mortality and to test the magnitude and direction of confounding, all All variables were included in the multivariable-adjusted analyses modelsto assess their independent effects on each LUTS. All characteristics were treated as time-dependent categorical variables in the regression model. “Last observation carried forward” method [16] was used for comorbidities with missing values in the following rounds. Parallel analyses were made for each LUTS to provide time-varying hazard ratios using variable values updated every five years (time-dependent analysis). To further examine the effect of fluctuation of LUTS and associated comorbidities, and for easier comparison to previous studies, sensitivity analyses were conducted using values of all variables fixed to the baseline assessment (1994) and Kaplan-Meier curves were used to graphically represent these associations. Furthermore, interaction terms were evaluated in the regression models of the association of each LUTS with mortality, and subgroup analyses were conducted for the variables with a significant interaction. For all statistical analyses, SPSS version 23 was used.

Results

A total of 2198 questionnaires (70 %) were returned in 1994, 2133 (75%) in 1999, 1905 (76%) in 2004 and 1424 (66%) in 2009 of whom 1332 were eligible for the study by providing sufficient data for the analyses, i.e. having answered questions regarding LUTS at every survey (while alive). Regarding the age distribution of the included men, the proportions were 41%, 36% and 23% for men aged 50, 60 and 70 at the baseline, respectively. Men with LUTS were generally older than those without LUTS and virtually all medical conditions were more frequent among men with LUTS (Table 1, Suppl. Table 1).

The symptoms showed substantial fluctuation with a decreasing trend for daytime frequency with a prevalence of 10.8% at the baseline and 7.3% at 15 years and an increasing trend for nocturia, with prevalence 3.8% at the baseline and 8.9% at 15 years. Reflecting the modified question in the assessment of urgency in 1994, its prevalence was materially lower at the baseline (1.8%) compared to the subsequent rounds (14.5% at five, 17.8% at 10 and 19.1% at 15 years) (Fig. 1).

Analyses of Mortality

During the 21-year follow-up, 514 men died, of whom 139 during the first, 126 during the second and 112 during the third 5-year period and 137 during the last period of six years. The overall mortality was 10.4% at five years, 19.9% at 10 years, 28.3% at 15 years and 38.6% at 21 years. Mortality was higher among men with LUTS at every stage of follow-up (Fig. 1). In unadjusted time-dependent analyses, each of the studied storage symptoms was strongly associated with an increased risk of death: the HR was 1.71 (95% CI 1.36-2.14) for urgency, 1.95 (1.52-2.49) for daytime frequency and 2.31

(1.79-2.98) for nocturia (Table 2). In unadjusted analyses with fixed baseline characteristics, daytime frequency and nocturia were significantly associated with an increased risk of death, while urgency showed no significant association: HR 1.43 (1.11-1.84) for daytime frequency, 2.56 (1.81-3.63) for nocturia and 1.52 (0.86-2.69) for urgency (Fig. 2, Table 2).

In multivariable-adjusted time-dependent analyses, daytime frequency and nocturia remained significantly associated with an increased risk of death, while urgency showed only a suggestive association: the adjusted HR was 1.42 (1.11-1.83) for daytime frequency, 1.38 (1.07-1.79) for nocturia and 1.19 (0.94-1.50) for urgency (Table 2, Suppl. Table 2). In multivariable-adjusted analyses with fixed baseline characteristics, only nocturia was suggestively associated with an increased risk of death: the adjusted HR was 0.94 (0.52-1.68) for urgency, 1.09 (0.84-1.42) for daytime frequency and 1.41 (0.99-2.02) for nocturia (Table 2, Suppl. Table 3).

In the regression analyses, the majority of the studied covariates – older age, marital status of single/divorced or widowed, current smoking, diabetes, cardiac disease, cerebrovascular disease, cancer and neurological disease – were indepedently associated with an increased risk of death (Suppl. Tables 2,3). In multivariable-adjusted analyses including interaction termsthe regression analysis, a significant interaction was found between smoking and urgency (p=0.02), as well as between previously diagnosed cardiac disease and urgency (p=0.04). The effect of urgency was suggestively stronger among non-smokers compared to smokers (HR 1.46, 1.12-1.91 vs. 0.73, 0.45-1.20) and among those without a diagnosed cardiac disease compared to those with a diagnosis (HR 1.30, 0.95-1.79 vs. 1.04, 0.73-1.48) (Table 3). The effects

of daytime frequency and nocturia showed no significant differences between any subgroups. (Suppl. Table 4).

Discussion

Due to the fluctuating nature of the symptoms and related comorbidities, the impact of LUTS as predictors of mortality has not been well established. The influence of short-term fluctuating symptoms can mask the effect of clinically relevant longer-term symptoms, compromising the reliability of the observed association of baseline LUTS on subsequent morbidity. To provide more robust estimates, we explored the impact of LUTS on mortality utilizing repeated assessments of these symptoms and associated comorbidities. Our results showed that men with nocturia or daytime frequency have increased mortality, even after adjustment for behavioral risk factors and comorbidities. However, the associations were significant only in analyses where the symptoms and comorbidities were updated every five years indicating that the baseline assessments of LUTS are reliable only in predicting short-term mortality risk while repeated assessments are needed to predict longer-term risk.

The crude death rates were higher in men with LUTS throughout the follow-up. After adjusting for age and comorbidities, daytime frequency and nocturia remained associated with mortality compared with men free of these symptoms. Although an association with mortality was more apparent for daytime frequency and nocturia than urgency, there was indication of an association of urinary urgency with an elevated death risk confined to non-smokers. In men with urinary urgency, and lacking the confounding effect of smoking — a commonly recognized risk factor for several illnesses such as cardiovascular diseases — the mortality risk was nearly 1.5-fold. Furthermore, we found an indication of urgency being related to increased mortality in men without a history of cardiac disease, which suggests that urgency might deserve attention as a potential indicator of latent heart disease.

Our study provides three important improvements to previous reports of longitudinal associations of LUTS with mortality. Firstly, we are not aware of any former study utilizing repeated assessments and thus taking into account the fluctuation and development of symptoms and comorbidities during follow-up. Secondly, our follow-up is longer than in any previous study on the topic, and covers more than 500 deaths (including >70 deaths among men with each of the LUTS examined). Thirdly, although some previous studies have assessed the impact of nocturia and urgency on mortality [8,17], we are not aware of any earlier study assessing mortality in relation to daytime frequency. Our effect size for mortality associated with nocturia is consistent with most previous studies showing, on average, a 1.3-fold risk [8]. Similarly, the magnitude of risk associated with urgency is fairly consistent with a previous Finnish study of elderly men reporting a 1.9-fold mortality at 10-year follow-up [17].

Regarding the limitations of the study, the nocturia question in DAN-PSS-1 does not distinguish one void from two voids per night. Because one nocturnal voiding is often considered normal, one or two voids/night are unlikely to distinguish meaningful nocturia and thus, ≥3 voids/night was considered a more robust indicator of important nocturia. Accordingly, while previous studies for aging men have predominantly used a nocturia case definition of ≥2 vs. 0-1 voids/night in their assessments of mortality, fairly consistently showing a nocturia-related excess risk of [8], a previous studya previous study did not show a significant association for one nocturnal void with mortality or significant gradient in relative death risk in men with three or more compared to those with two voids per night [18]. suggested a gradient in risk of death

with nocturia severity [18]. Furthermore, although incidence of nocturia is independent of nocturia case definition (≥1, ≥2, or ≥3 voids/night), remission frequency increases with more stringent criteria [9]. Due to a more stringent case definition in our analyses, remission over time is more likely and repeated assessments are therefore crucial.

Due to the relatively small number of deaths related to specific symptoms, our study did not have adequate statistical power to analyse the impact of multiple LUTS in combination. However, previous findings suggest that storage symptoms frequently overlap and various LUTS are often concomitant [19]. Furthermore, we were unable to assess the effect of treatments of LUTS on death. However, few men seek treatment for their LUTS [19,20] and response to treatment can be unsatisfactory particularly for storage symptoms [2,3,21]. Finally, some residual confounding in our results is likely in spite of extensive adjustments with various medical conditions and lifestyle factors.

While urinary symptoms are common in aging men, they may also be markers of ill health. Investigations for underlying comorbidity are warranted particularly in cases of persistent and treatment-resistant symptoms. The multifactorial etiology of LUTS includes various medical conditions and behavioural factors, besides age-related changes in the lower urinary tract such as development of BPH. Although LUTS share common etiologic factors, distinction between specific symptoms is important due to the different pathophysiologic mechanisms, especially in nocturia, which has been recently recognized as a separate clinical entity [22]. The proposed etiologies underlying various LUTS include vascular insufficiency of the pelvic floor due to atherosclerosis [23,24], systemic inflammation in metabolic syndrome [25],

neurogenic dysfunction related to diabetes [26], fluid shifts caused by hypertension and cardiac failure [27] as well as increased sympathetic activity caused by hyperinsulinemia or sleep problems [26,28]. These complex pathways may explain the association of LUTS with increased mortality. However, the evidence on the usefulness of various LUTS as causal risk factors for mortality is lacking: there is no data available on whether treatment of LUTS would decrease mortality e.g. by preventing injuries or cardiovascular events to occur [6,7,29].

In men aged over 50, the fluctuation of LUTS is common and often relates to benign and treatable conditions such as BPH. Respectively, men with persisting symptoms are likely to have comorbidities, causing resistance to urological treatments. Although various treatments for LUTS have potential to improve the quality of life of elderly male patients, care should be taken not to focus only on treating the symptoms but also exporing their general health. Besides having a potential impact on patients' prognosis, interventions for comorbidities and unhealthy lifestyle factors may also help LUTS to resolve.

In conclusion, LUTS are more accurate predictors of short-term than longer-term mortality risk among aging men. Repeated assessments are needed to identify clinically relevant and persistent symptoms, often associated with ill health. Accordingly, middle-aged and elderly men presenting with daytime frequrency or nocturia are potentially at a 1.4-fold increased risk of death. Therefore, the management of men with LUTS should focus not only on treating the symptoms, but also assessing their general health, risk factors and major comorbidities, including pre-clinical conditions.

Supplementary information is available at PCAN’s website.

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Conflicts of Interest

Jonne Åkerla has attended scientific congress as a guest for Sanofi. Jori Pesonen has received an unrestricted grant from Ferring, a lecture honorarium from Astellas, Merck and Orion and attended scientific congresses as a guest for Astellas, Novartis and Orion. Jukka Häkkinen has attended scientific congresses as a guest for Astellas and Orion. Teuvo Tammela worked as a consultant for Astellas, Orion Pharma, Bayer AG, Jansse-Cilag and as an investigator in clinical trials sponsored by Medivation, Orion Pharma, Bayer AG, Pfizer, Janssen-Cilag and Lidds Ab. Anssi Auvinen has been expert advisor for Epid Research Inc.

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Legends of figures and tables

Figure 1. Flow chart of mortality rates of men in relation to baseline prevalences and periodic incidence and remission rates of urinary urgency, frequency and nocturia.

Figure 2. Kaplan-Meier curves for men with and without daytime frequency and nocturia at the baseline (1994).

Table 1. Characteristics of men with and without urgency, daytime frequency and nocturia at the follow-up midpoint (2004).

Table 2. Unadjusted and adjusted association of LUTS with all-cause mortality in Cox regression analyses using variable values updated every five years (time-dependent analysis) and values fixed to the baseline assessment of 1994 (fixed analysis) during 21-year follow-up.

Table 3. Subgroup analyses for variables with significant interaction in the regression models: association of urinary urgency with mortality among smoking and non-smoking men and among men with and without previously diagnosed cardiac disease.

Supplementary files:

Suppl. Table 1. Characteristics of men at various stages of follow-up.

Suppl. Table 2. Unadjusted and adjusted association of LUTS and covariables with all-cause mortality in the follow-up of 21 years – Cox regression analyses with variable values updated every five years (time-dependent analysis).

Suppl. Table 3. Unadjusted and adjusted association of LUTS and covariables with all-cause mortality in the follow-up of 21 years - Cox regression analyses with variable values fixed to the baseline assessment of 1994 (fixed analysis).

Suppl. Table 4. *P*-values of interaction terms in regression analyses of the association of LUTS with all-cause mortality.

Tables

Table 1. Characteristics of men with and without urgency, daytime frequency and nocturia at the follow-up midpoint (2004).

	Urgency				**Daytime frequency**				**Nocturia**			
	Yes		No		Yes		No		Yes		No	
	n	%	n	%	n	%	n	%	n	%	n	%
Number of men	190		877		82		985		100		967	
Year of birth												
1944	66	34.7	432	49.5	34	41.5	464	47.1	25	25.0	473	48.9
1934	84	44.2	328	37.4	33	40.2	379	38.5	44	44.0	368	38.1
1924	40	21.1	117	13.3	15	18.3	142	14.4	31	31.0	126	13.0
Marital status												
Married/cohabiting	148	77.9	717	81.8	63	76.8	802	81.4	81	81.0	784	81.1
Single/divorced	33	17.4	111	12.7	15	18.3	129	13.1	15	15.0	129	13.3
Widowed	9	4.7	49	5.6	4	4.9	54	5.5	4	4.0	54	5.6
BMI												
≤25	60	31.6	289	33.0	21	25.6	328	33.3	36	36.0	313	32.4
25-30	89	46.8	431	49.1	39	47.6	481	48.8	51	51.0	469	48.5
>30	41	21.6	157	17.9	22	26.8	176	17.9	13	13.0	185	19.1
Current smoking	28	14.7	121	13.8	9	11.0	140	14.2	12	12.0	137	14.2
Alcohol intake >150 g/week	38	20	134	15.3	8	9.8	164	16.6	8	8.0	164	17.0
Medical conditions												
Diabetes	35	18.4	93	10.6	15	18.3	113	11.5	15	15.0	113	11.7
Hypertension	101	53.2	391	44.6	47	57.3	445	45.2	46	46.0	446	46.1
Cardiac disease	60	31.6	188	21.4	26	31.7	222	22.5	32	32.0	216	22.3
Pulmonary disease	27	14.2	99	11.3	8	9.8	118	12.0	19	19.0	107	11.1
Cerebrovascular disease	16	8.4	48	5.5	9	11.0	55	5.6	8	8.0	56	5.8
Cancer	22	11.6	79	9.0	8	9.8	93	9.4	18	18.0	83	8.6
Neurological disease	13	6.8	27	3.1	5	6.1	35	3.6	6	6.0	34	3.5

Table 2. Unadjusted and adjusted association of LUTS with all-cause mortality in Cox regression analyses using variable values updated every five years (time-dependent analysis) and values fixed to the baseline assessment of 1994 (fixed analysis).

		Urgency		**Frequency**		**Nocturia**	
		HR	95% CI	HR	95% CI	HR	95% CI
Time-dependent analysis	Unadjusted	1.71	1.36-2.14	1.95	1.52-2.49	2.31	1.79-2.98
	Adjusted [a]	1.19	0.94-1.50	1.42	1.11-1.83	1.38	1.07-1.79
Fixed analysis	Unadjusted	1.52	0.86-2.69	1.43	1.11-1.84	2.56	1.81-3.63
	Adjusted [b]	0.94	0.52-1.68	1.09	0.84-1.42	1.41	0.99-2.02

[a] A regression model including the year of birth and following categorical variables with time-varying values: LUTS, marital status, BMI, smoking, alcohol consumption, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer. "Last observation carried forward" method [14] used for comorbidities with missing values in the follow-up rounds.

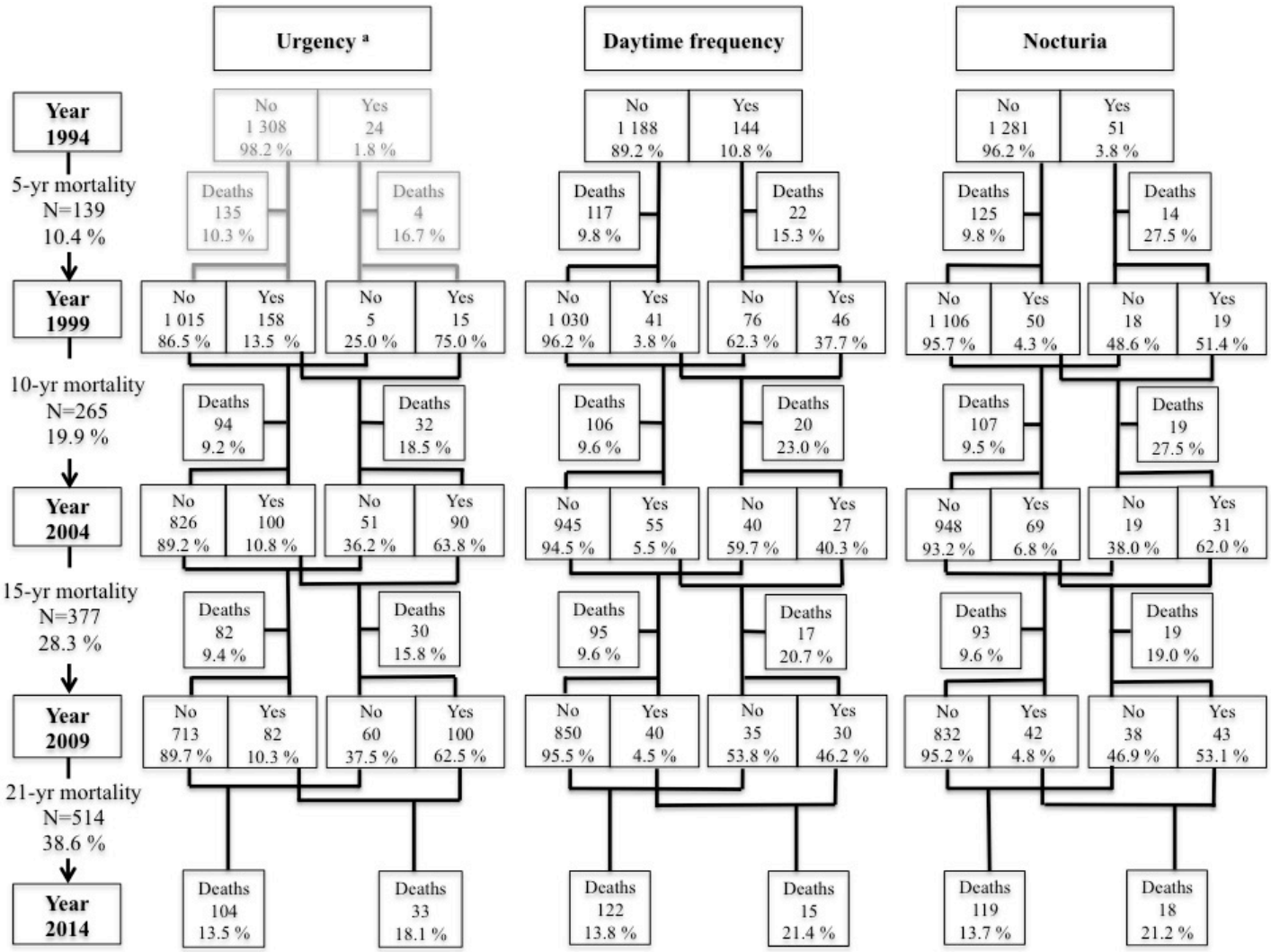
[b] All above-mentioned variables treated as fixed categorical variables in the regression model i.e. the variable values fixed to the baseline assessment of 1994.

Table 3. Subgroup analyses for variables with significant interaction in the regression models: association of urinary urgency with mortality among smoking and non-smoking men and among men with and without previously diagnosed cardiac disease.

	Unadjusted		**Adjusted** [a]	
	HR	95% CI	HR	95% CI
Current smoking				
Yes	0.95	0.60-1.51	0.73	0.45-1.20
No	2.09	1.61-2.71	1.46	1.12-1.91
Cardiac disease				
Yes	1.20	0.86-1.69	1.04	0.73-1.48
No	2.11	1.55-2.86	1.30	0.95-1.79

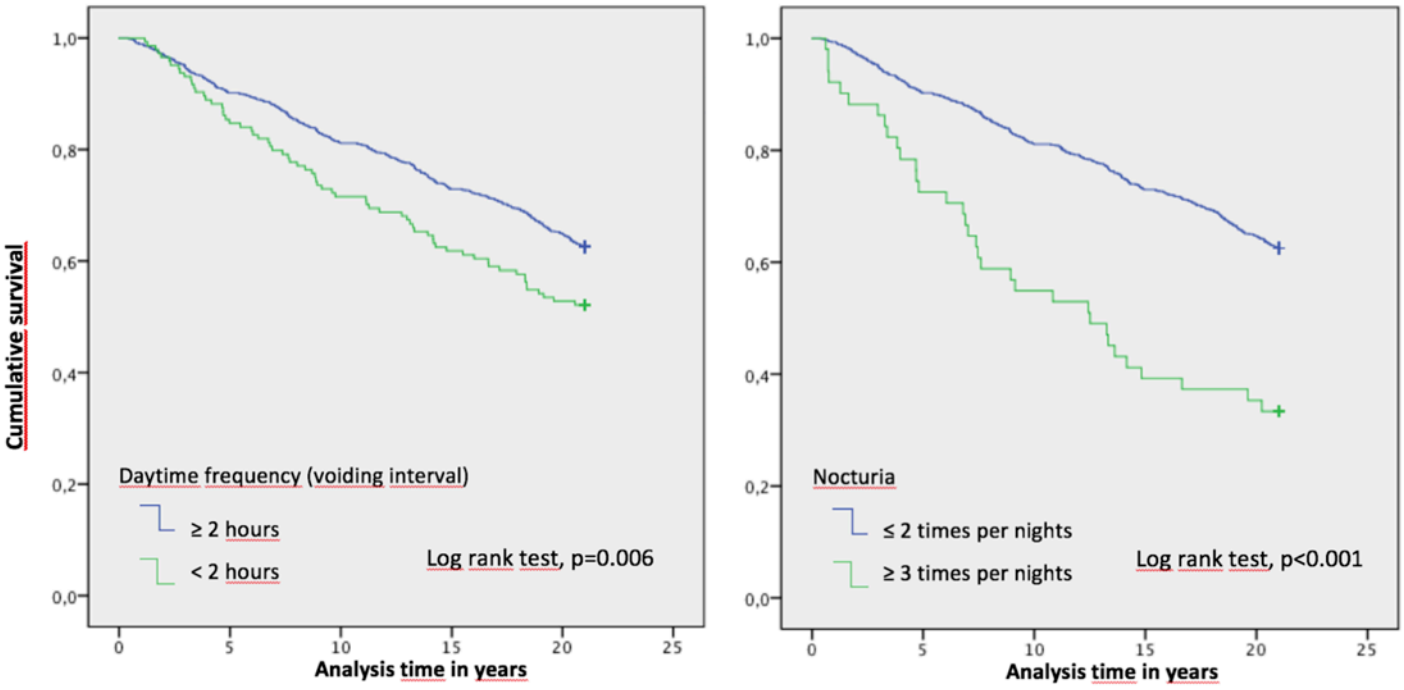
[a] A regression model including the year of birth and following categorical variables with time-varying values: LUTS, marital status, BMI, smoking, alcohol consumption, diabetes, hypertension, cardiac disease, pulmonary disease, cerebrovascular disease, neurological disease and cancer. “Last observation carried forward” method [14] used for comorbidities with missing values in the follow-up rounds.

Figure 1. Flow chart of mortality rates of men according to periodic LUTS status.



[a] Assessed with a modified question in 1994.

Figure 2. Kaplan-Meier curves for men with and without daytime frequency and nocturia at the baseline (1994).



Number at risk				Number at risk			
≥ 2 h	1 188	964	771	≤ 2	1 281	1 039	829
< 2 h	144	103	76	≥ 3	51	37	18